Efficacy and safety of iguratimod combined with methylprednisolone for primary Sjögren's syndrome: a meta-analysis and trial sequential analysis

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Abstract. – **OBJECTIVE:** The purpose of this study is to evaluate the combination of iguratimod (IGU) and methylprednisolone (MP) for the efficacy and safety of primary Sjögren's syndrome (pSS) by a meta-analysis and a trial sequential analysis (TSA).

MATERIALS AND METHODS: Clinical studies of IGU combined with MP for pSS were searched through eight databases. Revman 5.3 and TSA 0.9.5.10 Beta were used for the meta-analysis and TSA.

RESULTS: In terms of efficacy endpoints, compared with "HCQ+MP" group, "IGU+MP" group decreased erythrocyte sedimentation rate (ESR) [mean difference (MD)=-5.15, 95% confidence interval (CI)=(-7.37, -2.93), $p<0.0001$], immunoglobulin G (IgG) [MD=-3.38, 95% CI=(-4.13, -2.64), $p<0.00001$], immunoglobulin M (IgM) [MD=-0.64, 95% CI=(-1.19, -0.09), $p=0.02$], Immunoglobulin A (IgA) [MD=-1.16, 95% CI=(-1.92, -0.39), $p=0.003$], EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) [MD=-1.62, 95% CI=(-2.07, -1.17), $p<0.0001$], EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) [MD=-2.07, 95% CI=(-2.54, -1.59), $p<0.0001$], increase platelet (PLT) [MD=13.21, 95% CI=(9.77,16.65), $p<0.00001$], and improve Schirmer I test (SIT) [MD=1.86, 95% CI=(1.40, 2.32), $p<0.0001$]. TSA presented that these benefits observed with the current information volume were all conclusive, except for IgM. In terms of safety endpoints, the total adverse event rates (AEs), leucopenia, gastrointestinal (GI) AEs, skin diseases, and liver dysfunction of the "IGU+MP" group and the "HCQ+MP" group were comparable. And TSA indicated that the results need to be confirmed by additional studies. Harbord regression showed no publication bias ($p=0.986$).

CONCLUSIONS: IGU combined with MP effectively attenuates autoimmune responses (IgG, IgM, IgA), reduces clinical symptoms and disease activity (ESR, PLT, ESSPRI, ESSDAI), and improves the exocrine gland functional status (SIT) in patients with pSS. IGU combined with MP does not increase the risk of adverse events, which means that IGU combined with MP may be a safe and effective strategy for the treatment of pSS and has value for further research exploration.

Key Words:
   Iguratimod, Methylprednisolone, Primary Sjögren's syndrome, Meta-analysis, Trial sequential analysis, Harbord.

Introduction

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease characterized by lymphocyte proliferation and progressive damage to exocrine glands, and even systemic organ involvement[1,2]. pSS is a global disease with a prevalent age of 30-60 years and a high prevalence in women[3], and it is also the most common autoimmune disease in the middle-aged and elderly population. Epidemiological studies[4-6] have shown that the prevalence of pSS in the Chinese population is 0.33%-0.77%[4], ranking second in autoimmune diseases[5], while the global prevalence of pSS is only 43.69/100,000 to 77.94/100,000[6]. The clinical manifestations of pSS vary from mild to severe, ranging from local symptoms of dry mouth and eyes to multiple organ or systemic damage such as lung and kidney damage in severe cases[7-9]. pSS poses a serious threat to human physical and mental health[9]. More than 80% of patients with pSS are reported to have symptoms such as dryness, pain, and fatigue[4]. Patients also have a significantly increased risk of developing B-cell lymphoma[10]. The tremendous impact of pSS on patients has made it of broad and current

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interest. Since the etiology of pSS has not been elucidated, there are no specific targeted drugs for this disease. At present, pSS is primarily managed through empirical treatment methods or by utilizing available treatment options, and its clinical treatment plan needs to be phased according to the patient's overall symptoms and the degree of organ damage for long-term treatment[7]. Topical replacement therapy is the main means of intervention for pSS. Traditional anti-rheumatic drugs and immunosuppressive agents, including hydroxychloroquine (HCQ), methylprednisolone (MP), mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, are still considered to be the most prominent agents for the relief of extraglandular symptoms in patients with pSS, but their efficacy is more limited[7,11]. In addition, the high price of biological agents has discouraged some patients, while the emergence of new drugs is urgently needed.

Iguratimod (IGU) is a novel small molecule compound with anti-inflammatory and immunomodulatory effects, which was previously primarily utilized for rheumatoid arthritis[13]. It has been noted that IGU can inhibit the production of cytokines [interferon-gamma (IFN-γ), interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), etc.] and suppress the activation of B lymphocytes, thus effectively reducing the immune inflammatory response[14]. Nowadays, IGU has been used in the clinical treatment of rheumatoid arthritis. It has been reported that IGU can improve disease activity and laboratory indices in patients with early pSS[15], which is expected to be a novel drug for the treatment of pSS. IGU is the basic drug recommended by international guidelines for pSS[16]. However, patients with a strong inflammatory reaction and high disease activity often need a combination therapy of hydroxychloroquine and MP[16], due to the limited efficacy of HCQ[11]. As an adrenal glucocorticoid, MP has obvious anti-inflammatory effect[17] and can effectively relieve the clinical symptoms of patients with pSS, which is often used as a concomitant of combined drugs[18]. More and more evidence[19-20] showed that the combination of IGU and MP may be an effective strategy for the treatment of pSS. Therefore, this study evaluated the specific benefits of IGU combined with MP by using a meta-analysis and a trial sequential analysis (TSA), in order to provide theoretical basis and clinical evidence for the use of IGU combined with MP in pSS.

Materials and Methods

This study strictly followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) for systematic reviews and meta-analysis methods[21].

Search Strategies

Two investigators independently searched for clinical studies on iguratimod combined with methylprednisolone for primary Sjögren's syndrome, and the third investigator decided in case of a dispute. A total of four Chinese databases [China National Knowledge Infrastructure (CNKI), China Biology Medicine (CBM), VIP and Wanfang], and four English databases (Embase, PubMed, the Cochrane Library and Web of Science databases) were searched. The search literature was published until February 2023, with no restrictions on region. The English subject heading covered iguratimod, methylprednisolone, and primary Sjögren's syndrome. The Chinese subject heading covered "ailamode" (Chinese name for iguratimod), "jiaponilong" (Chinese name for methylprednisolone), "yuanfaxing ganzao zonghezheng" (Chinese name for primary Sjögren's syndrome). On the basis of subject headings, CNKI and CBM database were applied to expand Chinese free terms, MeSH database was employed to expand English free terms, and then subject headings and free terms were combined for retrieval.

Inclusion and Exclusion Criteria

The inclusion criteria for the literature were as follows. 1) Study design – randomized controlled trial. 2) Participants – consistent with the basic diagnosis of pSS[22-24]. 3) Intervention – participants in the experimental group were given IGU and MP, and patients in the control group were given HCQ and MP. 4) Outcomes – immunoglobulin G (IgG), immunoglobulin M (IgM), immunoglobulin A (IgA), erythrocyte sedimentation rate (ESR), platelet (PLT), EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), Schirmer I test (SIT) were adopted as efficacy endpoints, and adverse event rates (AEs), leucopenia, gastrointestinal (GI) AEs, skin diseases, and liver dysfunction were taken as safety endpoints.

The exclusion criteria were as follows. 1) Non-randomized controlled trials. 2) Studies published repeatedly. 3) Studies published as abstracts. 4) Studies with incomplete or unclear data.

Data Extraction

Relevant literature retrieved from the various databases was imported into Endnote X9 software (The Thomson Scientific, Stanford, Connecticut, USA), and after reviewing the title, abstract, and full text of the literature, any articles that did not meet the inclusion criteria were eliminated to determine the final selection. The included literature was categorized and organized, and the essential characteristics were mapped into a statistical table of information. The risk of bias was appraised using the Cochrane Risk of Bias Assessment Tool(MRC Biostatistics Unit, Institute of Public Health, Cambridge CB2 0SR, UK) according to the required entries. All work was independently undertaken by two investigators, and any discrepancy was adjudicated by a third investigator.

Statistical Analysis

When performing data analysis with Revman 5.3 software (Review Manager Web, The Cochrane Collaboration, Copenhagen, Denmark), relative risk (RR) was used to assess dichotomous variables. For continuous variables, mean difference (MD) was used when the outcomes were in consistent units, and standard mean difference (SMD) was used when the outcomes were not in consistent units. All indicators must be analyzed using 95% confidence intervals (95% CI).

Heterogeneity was analyzed by I^2 test and Q test. If $I^2 < 50\%$ and $p > 0.1$, heterogeneity was small, and fixed-effects model (FEM) analysis was employed. Otherwise, a random effects model (REM) analysis was conducted. Sensitivity analysis was performed on indicators with $I^2 > 50\%$ to test whether the results were stable. TSA 0.9.5.10 Beta software (The Copenhagen Trial Unit, Copenhagen, Denmark and Stata Corp LLC Texas, USA) 15.0 software) was used for trial sequential analysis to clarify whether the results were conclusive. Publication bias was evaluated using Stata 15.0 software, and a $p > 0.1$ indicated that there was no publication bias. Quality evaluation of the evidence was completed using GRADEpro 3.6 software (McMaster University, Hamilton, ON, Canada).

Results

Research Selection

A total of 192 studies were obtained from the search, of which 129 were excluded as duplicates. After reading the title, abstract and full text, 52 studies were removed. Finally, 11 studies were integrated. The flow chart is shown in Figure 1.

Primary Materials

A total of 11 clinical studies[25-35] were enlisted with a total sample size of 946 cases, 473 in the experimental group and 473 in the control group. The research centers were all in China. The female ratio ranged from 42.68% to 100%. The mean age varied between 36.50 years and 72.68 years. The average duration of the disease lay between 27.06 months to 184.32 months (Table I).

Risk of Bias Assessment

Of the 11 incorporated studies, 3 studies[28,31,35] had an unclear risk of randomization, 10 studies[25-26,28-35] had an unclear risk of allocation concealment. Intervention blinding was high risk in all 11 studies. Deviation in the remaining areas is low risk (Figure 2).

Efficacy Endpoints

IgG, IgM, IgA

Compared with "HCQ+MP" group, the meta-analysis demonstrated that the "IGU+MP" group could significantly reduce IgG by 3.38 g/L [MD=-3.38, 95% CI=(-4.13, -2.64), $p < 0.00001$], IgM by 0.64 g/L [MD=-0.64, 95% CI=(-1.19, -0.09), $p=0.02$] and IgA by 1.16 g/L [MD=-1.16, 95% CI=(-1.92, -0.39), $p=0.003$]. Sensitivity analysis showed that there was no significant change in the results of each combination, suggesting that the results were robust. TSA revealed that the results observed for the current information set were conclusive, with the exception of IgM. The GRADE evaluation showed a very low quality of evidence for IgG and low quality of evidence for IgM and IgA (Figure 3).

ESR, PLT

Compared with "HCQ+MP" group, the meta-analysis demonstrated that the "IGU+MP" group could significantly reduce ESR by 5.15 mm/h [MD=-5.15, 95% CI=(-7.37, -2.93), $p < 0.0001$], and increase PLT by 13.21×10^9/L [MD=13.21, 95% CI=(9.77,16.65), $p < 0.00001$]. Sensitivity analysis showed that there was no significant change in the results of each combination, suggesting that the results were robust. TSA indicated that the benefits observed for the current information set were conclusive. The GRADE evaluation showed low-quality evidence for ESR, and moderate-quality evidence for PLT (Figure 4).
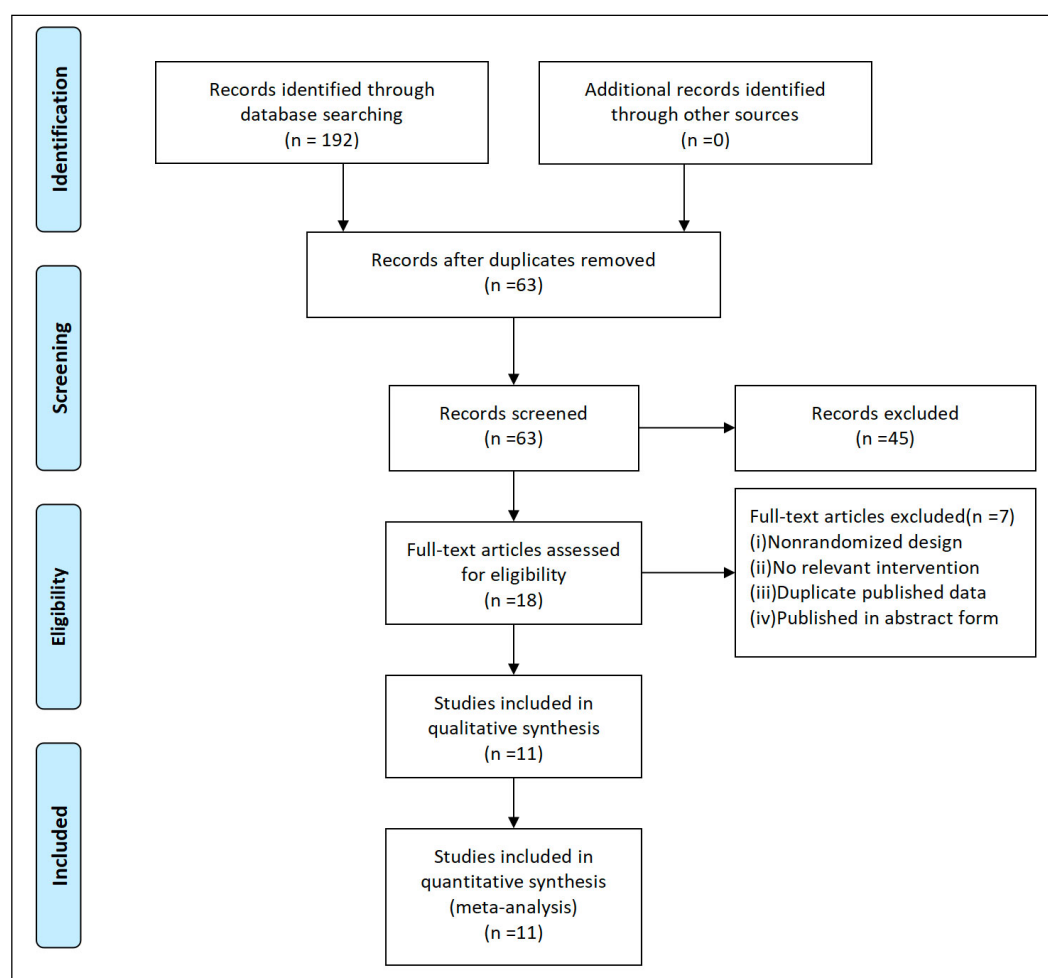
Figure 1. Flow diagram.

ESSDAI, ESSPRI

Compared with "HCQ+MP" group, the meta-analysis demonstrated that the "IGU+MP" group could significantly reduce ESSDAI by 1.62 [MD=-1.62, 95% CI=(-2.07, -1.17), $p<0.0001$] and ESSPRI by 2.07 [MD=-2.07, 95% CI=(-2.54, -1.59), $p<0.0001$]. Sensitivity analysis showed that there was no significant change in the results of each combination, suggesting that the results of ESSPRI were robust. TSA showed that the benefits observed for the current information set were conclusive. The GRADE evaluation showed moderate-quality evidence for ESSDAI, and low-quality evidence for ESSPRI (Figure 5).

Schirmer I Test

Compared with "HCQ+MP" group, the meta-analysis demonstrated that the "IGU+MP" group could significantly improve SIT by 1.86 mm/5 min [MD=1.86, 95% CI=(1.40, 2.32),

$p<0.0001$]. TSA indicated that the benefits observed in the current pool of information were conclusive. The GRADE evaluation showed moderate quality of evidence for SIT (Figure 6).

Safety Endpoint

Compared with "HCQ+MP" group, the meta-analysis demonstrated that total AEs [RR=0.70, 95% CI=(0.47, 1.03), $p=0.07$], leukopenia [RR=1.29, 95% CI=(0.48, 3.50), $p=0.61$], GI AEs [RR=0.76, 95% CI=(0.39, 1.46), $p=0.41$], skin diseases [RR=0.63, 95% CI=(0.31, 1.30), $p<0.0001$], liver dysfunction [RR=0.32, 95% CI=(0.09, 1.21), $p=0.09$] in the "IGU+MP" group were comparable. TSA revealed that none of the safety endpoints met the TSA threshold and expected information values, and the safety of IGU could still be demonstrated in future studies. The GRADE evaluation showed low-quality evidence for all of these indicators (Table II).

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Table I. Baseline characteristics of included studies.

Author	Year	Sample size (E/C)	Female N(%)	Average age (month)	Average disease duration (month)	Intervention and dose	Treatment duration
Jiang et al[25]	2016	30	30 (100%)	45.13±12.11	72.13±28.13	MP 8 mg qd IGU 25 mg bid	12 W
		30	30 (100%)	46.33±13.74	58.80±32.0	MP 8 mg qd HCQ 200 mg bid	
Xu et al[26]	2017	47	42 (89.4%)	44.50±13.20	73.40±21.80	MP 8 mg qd IGU 25 mg bid	12 W
		47	40 (85.1%)	45.30±13.10	71.50±20.80	MP 8 mg qd HCQ 200 mg bid	
Xia et al[27]	2017	50	50 (100%)	42.13±9.97	/	MP 8 mg qd IGU 25 mg bid	12 W
		50	50 (100%)	42.08±9.65	/	MP 8 mg qd HCQ 200 mg bid	
Luo et al[28]	2018	40	36 (90%)	43.60±10.50	/	MP 8 mg qd IGU 25 mg bid	12 W
		40	35 (87.5%)	45.20±12.90	/	MP 8 mg qd HCQ 200 mg bid	
Zhang and Shen[29]	2019	43	32 (74.4%)	40.50±9.41	27.72±7.32	MP 8 mg qd IGU 25 mg bid	12 W
		43	29 (67.4%)	41.03±10.01	26.40±6.24	MP 8 mg qd HCQ 200 mg bid	
Zhao[30]	2019	41	18 (43.9%)	54.52±6.54	54.36±10.08	MP 8 mg qd IGU 25 mg bid	12 W
		41	17 (41.5%)	55.51±6.52	42.6±10.32	MP 8 mg qd HCQ 200 mg bid	
Yu[31]	2020	38	22 (57.9%)	41.18±3.36	61.80±7.44	MP 8 mg qd IGU 25 mg bid	12 W
		38	21 (55.3%)	41.14±3.39	61.44±7.92	MP 8 mg qd HCQ 200 mg bid	
Zhuang[32]	2020	34	17 (50%)	36.48±1.25	/	MP 8 mg qd IGU 25 mg bid	12 W
		34	16 (47.1%)	36.51±1.19	/	MP 8 mg qd HCQ 200 mg bid	
Gu[33]	2020	40	16 (40%)	66.51±4.23	51.36±16.80	MP 8 mg qd IGU 25 mg bid	12 W
		40	17 (42.5%)	66.72±4.34	52.32±16.20	MP 8 mg qd HCQ 200 mg bid	
Gu[34]	2022	**42**	34 (81%)	41.56±10.21	29.76±8.64	MP 8mg qd IGU 25 mg bid	2 W
		42	33 (78.6%)	40.97±10.24	29.04±8.52	MP 8 mg qd HCQ 200 mg bid	
Li and Li[35]	2022	68	60 (88.2%)	72.71±12.59	184.56±96.60	MP 8 mg qd IGU 25 mg bid	12 W
		68	59 (86.8%)	72.65±12.62	184.08±96.24	MP 8 mg qd HCQ 200 mg bid	

E, experimental group; C, control group; N, number; W, week; IGU, iguratimod; MP, methylprednisolone; HCQ, hydroxychloroquine.
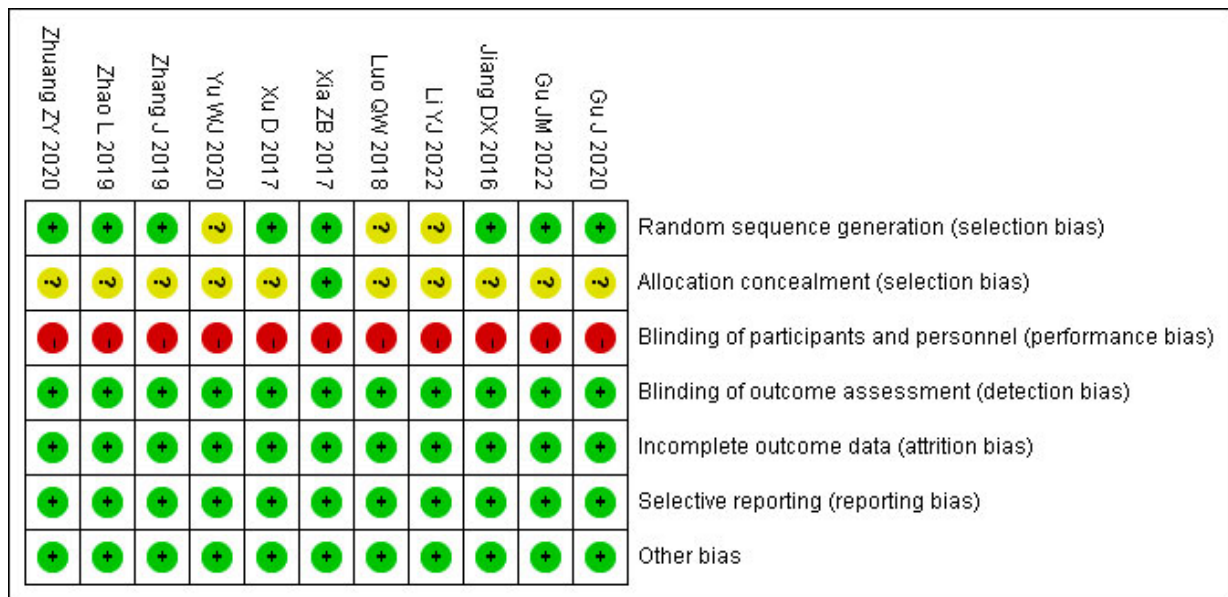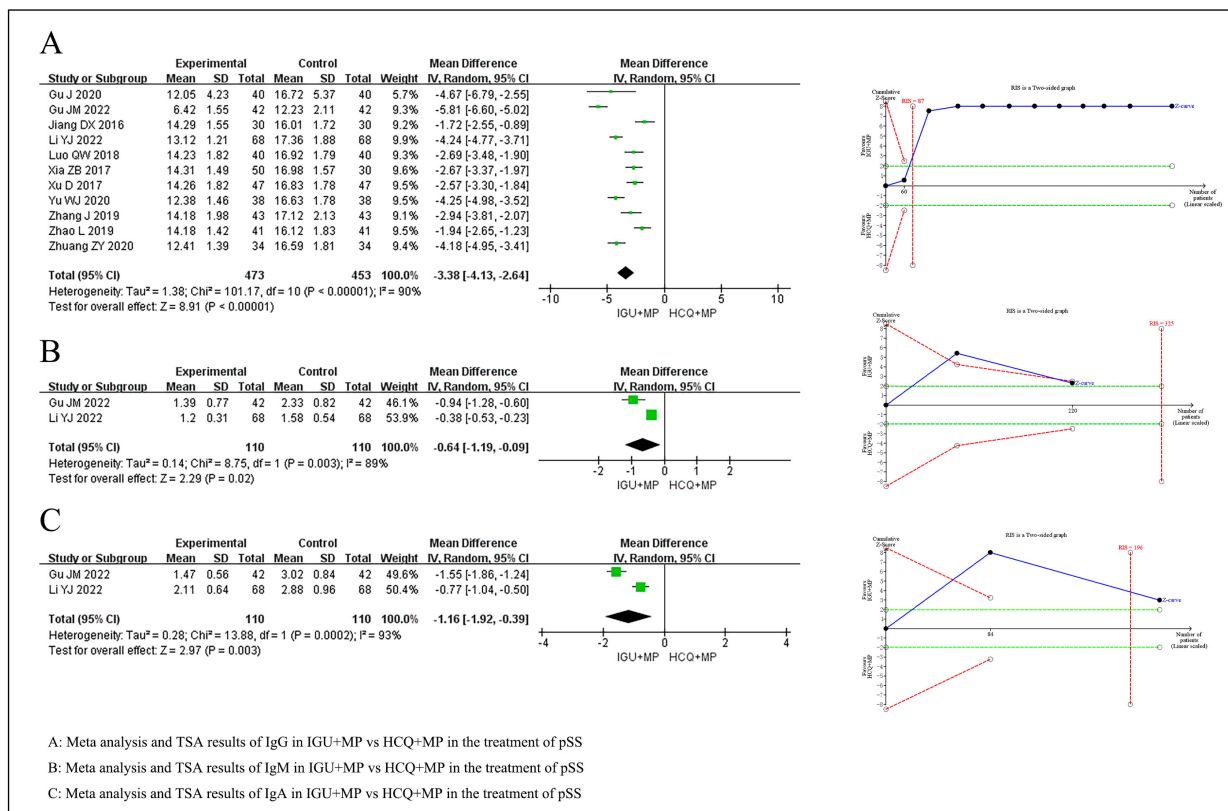
Figure 2. Risk of bias graph.

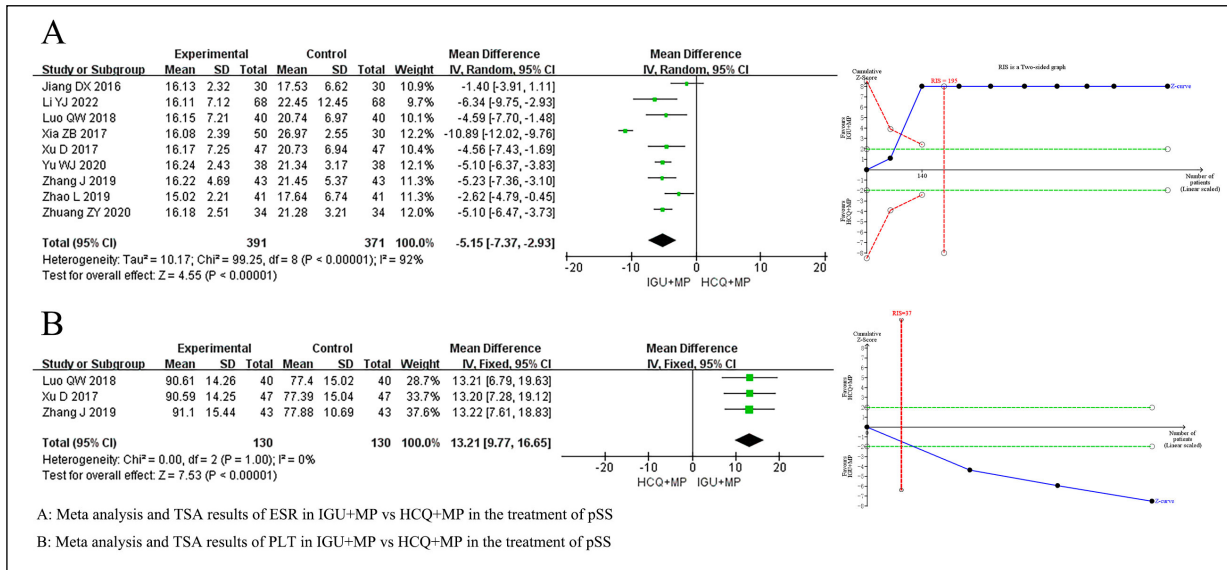A: Meta analysis and TSA results of IgG in IGU+MP vs HCQ+MP in the treatment of pSS

B: Meta analysis and TSA results of IgM in IGU+MP vs HCQ+MP in the treatment of pSS

C: Meta analysis and TSA results of IgA in IGU+MP vs HCQ+MP in the treatment of pSS

Figure 3. Meta-analysis and TSA results of IgG, IgM, IgA in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **A**, Meta-analysis and TSA results of IgG in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **B**, Meta-analysis and TSA results of IgM in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **C**, Meta-analysis and TSA results of IgA in IGU+MP *vs.* HCQ+MP in the treatment of pSS. TSA, trial sequential analysis; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; IGU, iguratimod; MP, methylprednisolone; HCQ, hydroxychloroquine; pSS, primary Sjögren's syndrome.

Figure 4. Meta-analysis and TSA results of ESR, PLT in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **A**, Meta-analysis and TSA results of ESR in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **B**, Meta-analysis and TSA results of PLT in IGU+MP *vs.* HCQ+MP in the treatment of pSS. TSA, trial sequential analysis; ESR, erythrocyte sedimentation rate; PLT, platelet; IGU, iguratimod; MP, methylprednisolone; HCQ, hydroxychloroquine; pSS, primary Sjögren's syndrome.
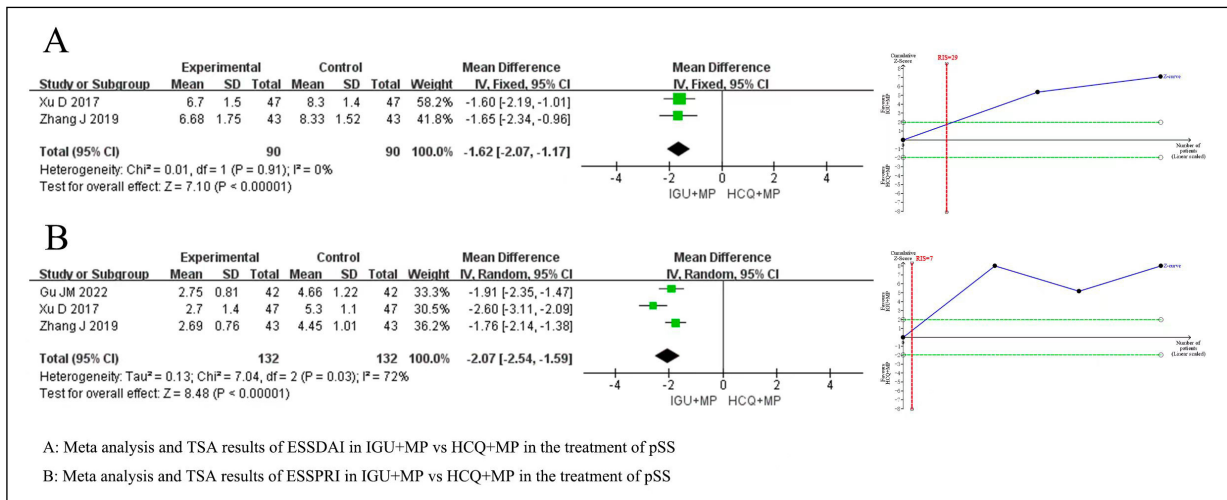

Figure 5. Meta-analysis and TSA results of ESSDAI, ESSPRI in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **A**, Meta-analysis and TSA results of ESSDAI in IGU+MP *vs.* HCQ+MP in the treatment of pSS. **B**, Meta-analysis and TSA results of ESSPRI in IGU+MP *vs.* HCQ+MP in the treatment of pSS. TSA, trial sequential analysis; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI, EULAR Sjögren's Syndrome Patient Reported Index; IGU, iguratimod; MP, methylprednisolone; HCQ, hydroxychloroquine; pSS, primary Sjögren's syndrome.
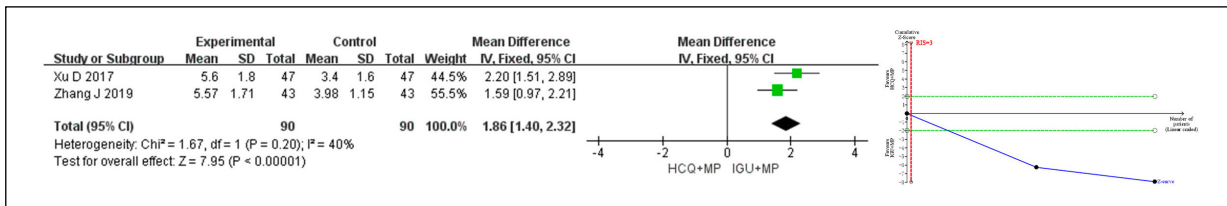

Figure 6. Meta-analysis and TSA results of SIT in IGU+MP *vs.* HCQ+MP in the treatment of pSS. TSA, trial sequential analysis; SIT, Schirmer I test; IGU, iguratimod; MP, methylprednisolone; HCQ, hydroxychloroquine; pSS, primary Sjögren's syndrome.

Table II. Meta-analysis and TSA results of IGU+MP *vs.* HCQ+MP for AEs.

Outcome	IGU+MP (events/total)	HCQ+MP (events/total)	I^2	RR (95% CI)	TSA	RIS
Total AEs	37/351	53/351	0	0.70 (0.47, 1.03)	NO	1688
leukopenia	6/309	4/309	0	1.29 (0.48, 3.50)	NO	11808
GI AEs	17/280	22/280	0	0.76 (0.39, 1.46)	NO	6350
skin diseases	12/351	19/351	0	0.63 (0.31, 1.30)	NO	3346
liver dysfunction	2/170	8/170	0	0.32 (0.09, 1.21)	NO	721

RR, Risk ratio; TSA, Trial sequential analysis; RIS, required information size; AEs, adverse events; GI, gastrointestinal; IGU, iguratimod; MP, methylprednisolone; HCQ, hydroxychloroquine.
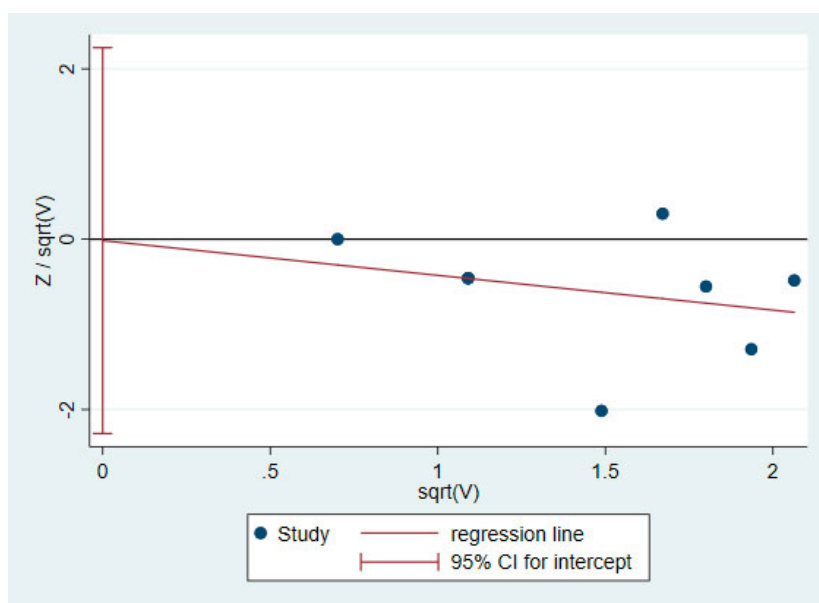

Figure 7. Publication bias assessment graph.

Publication Bias

Harbord regression of total AEs displayed no appreciable publication bias (*p*=0.986) (Figure 7).

Discussion

A total of 11 clinical studies and 946 sample sizes were integrated into this meta-analysis and TSA. Sensitivity analysis, TSA, and quality of evidence evaluation gave a more comprehensive and credible result for our study. These analyses confirmed the benefit and safety of IGU combined with MP in the treatment of pSS.

Our meta-analysis revealed that "IGU+MP" group significantly reduced IgG, IgA, and IgM levels in patients with pSS, and TSA supported that the benefits in IgG and IgA were conclusive. This evidence demonstrates that the mechanism of IGU interfering with pSS from the B-cell level suppresses the autoimmune response, thereby reducing the formation of autoantibodies such as IgG, IgA, IgM. The results of the meta-analysis also disclosed that "IGU+MP" group significantly reduced ESR level, and increased PLT level compared with "HCQ+MP". TSA hinted that the benefits were conclusive. The benefit in ESR, PLT levels in the "IGU+MP" group suggests that IGU is effective in reducing the inflammatory response in patients with pSS, and that IGU may enhance the anti-inflammatory effects of MP through synergistic or independent pathways. The increase in PLT level may be related to IGU's inhibition of autoimmune responses and allevi-

ation of antibody attacks on platelets. The ESS-DAI and ESSPRI scores are commonly utilized to evaluate pSS disease activity as well as subjective patient symptoms[36-37]. And they have become indicators to quantify pSS disease activity, and both are often used in conjunction with each other[36]. The meta-analysis confirmed the benefit of the "IGU+MP" group in improving ESSPRI and ESSDAI, and TSA proved the benefit of ESSPRI and ESSDAI to be conclusive. This evidence illustrates that "IGU+MP" group is effective in lessening clinical symptoms and reducing disease activity in patients with pSS, and these effects may be related to its mechanism of suppressing the autoimmune and inflammatory responses. SIT is an important indicator of the functional status of the exocrine glands and can be used to diagnose pSS and assess disease progression[38]. The meta-analysis displayed that, relative to the "HCQ+MP" group, "IGU+MP" group had higher SIT results. This implies that IGU combined with MP can promote exocrine gland secretion, which reduces exocrine gland symptoms such as dry mouth and dry eyes.

The autoimmune response and autoantibody formation are central to the development of pSS. IGU is able to alleviate exocrine symptoms and reduce disease activity in patients with pSS by suppressing autoimmune and inflammatory responses, a process that may be associated with B lymphocytes[39]. The immunopathogenesis of pSS is a complex process associated with both the innate and adaptive immune systems[40], and B lymphocytes play a key role in this process[41,42]. B-cell abnormalities in patients with pSS are mainly manifested by increasing germinal center B cells and plasma cells in peripheral blood, decreasing memory B cells[41,43]. Moreover, the germinal center-like structures visible in salivary glands, and increased CD138+ plasma cells[41,43]. B-cell hyperactivity and peripheral blood B-cell disturbance appear to be characteristic of the disease[44,45]. In addition, abnormalities such as B-cell maturation, development, and immune tolerance are also closely related to pSS, and these factors together cause the disturbance of the immune system[43]. BAFF, as a B-cell activator, is a positive regulator of B-cell activation and antibody production[36]. BAFF is central to the cross-talk between early activation of the innate immune system and auto-reactive B-cell stimulation[36]. In autoimmune diseases, autoreactive B cells are activated due to exposure to endogenous autoantigens, and BAFF accelerates this process, inducing excess produc-

tion of IgG and autoantibodies[46]. The number of these autoantibody-producing plasma cells was positively correlated with serum IgG levels, disease activity, and autoantibody positivity[47]. Shao et al[36] found that IGU-treated patients with pSS had lower BAFF levels and plasma cell percentages relative to placebo, which implies that the mechanism of IGU intervention in pSS may be related to the inhibition of BAFF-mediated autoimmune responses. In fact, the inhibitory effect of IGU on BAFF was observed as early as in animal experiments in MRL/lpr mice[48]. Some studies[49,50] have also reported the ability of IGU to reduce BAFF levels in the blood of patients with igg4-related diseases. In addition, IGU also reduces the count of peripheral plasma cells and antibody levels in patients with rheumatoid arthritis[50]. It has also been shown that IGU is able to inhibit immunoglobulin production by B cells through regulation of the protein kinase C/early growth response factor 1 (PKC/EGR1) pathway[50]. IGU also represses the production of inflammatory factors by inhibiting the nuclear factor-kappa B (NF-**κB**) signaling pathway[50]. IgG, IgM, and IgA are common immunoglobulin factors, which reflect the expression of the body's immunoglobulins[34,51]. In general, patients with pSS have significantly elevated levels of immunoglobulins, mainly IgG, which are positively correlated with disease activity[50]. Therefore, inhibiting the excessive activation of B cells and reducing the production of immunoglobulins has become the key to treating pSS[51]. Specifically, IGU may reduce the activated expression of some B-cell subsets (CD19+, CD27+, CD38+), and attenuate the pathological effects of B cells and exocrine glandular infiltration[53-55]. In addition, IGU also can reduce autoantibody and immunoglobulin levels (IgG, IgM, IgA) by inhibiting the binding of BAFF to its receptors[53-55]. This, in turn, reduces autoimmune and inflammatory damage.

In terms of safety endpoints, the meta-analysis indicated that the total AEs, leucopenia, skin diseases and liver dysfunction in the "IGU+MP" group were comparable to those in the "HCQ+MP" group. This implies that IGU combined with MP will not pose additional safety risks. However, TSA reveals that the security endpoint of the current pool of information observed has not reached the expected information value, Therefore, due to the limitations of the study base and total sample size, the safety of "IGU+MP" still needs to be further explored in follow-up studies.

Although our study strictly followed the PRISMA-P for systematic reviews and meta-analysis methods, the study still has some limitations. First, the small sample size of the included studies would reduce the credibility of the study results. In turn, relaxing the inclusion criteria would increase the risk of bias in the study results. Second, 3 studies[28,31,35] in the included literature had unknown risks of randomization methods, and 10 studies[25-26,28-35] had unknown risks of concealed protocols. And all studies had a high risk of intervention blinding, which led to some methodological heterogeneity and may have affected the credibility of the results. Third, there is a significant clinical heterogeneity. 1) There were differences in inclusion criteria in the included studies. The diagnostic criteria relate to the 2002 European League Against Rheumatism criteria[22], the 2012 American College of Rheumatology criteria[23], and the 2016 American College of Rheumatology/European League Against Rheumatoid criteria[24]. 2) Narrow inclusion criteria would limit the readability of the results. Xu et al[26] limited the inclusion criteria to patients with PLT≤80×10^9/L, and Gu[33] subjectively only included subjects aged 50-80. Meanwhile, all studies had a much higher percentage of female patients, except for Zhao[30], Yu[31] Zhuang[32], and Gu[33]. In addition, the study centers of all studies were in China. This means that the results of this study apply mainly to Chinese women, while the effect of IGU+MP on Chinese men and other Asians, European-Americans, and Africans is not fully known. 3) There was variation in the choice of efficacy endpoints. ESSPRI scores and ESSDAI scores are important measures of pSS progression. However, the efficacy endpoints in eight studies[25,27,28,30-33,35] did not involve them. 4) Lack of long-term follow-up data. IGU combined with MP can effectively relieve clinical symptoms in patients with pSS in the short term, but patients with pSS often require long-term treatment. Thus, the long-term efficacy of ICU combined with MP is also extremely important. In the included literature, the follow-up time of the study by Gu34 was 2 weeks, and the follow-up time of the rest was 12 weeks. This implies that the data obtained in this study are mostly for short-term efficacy, and there is still a lack of data from studies evaluating long-term efficacy.

In view of these limitations, we expect that future research can continue to improve. First of all, increase the sample size and conduct strict randomized controlled double-blind trials to improve the accuracy of research results further, reduce the potential heterogeneity of methods, and increase the reliability of results. Secondly, control relevant variables to conduct stratified study to explore the impact of IGU combined with MP on pSS patients of different ages and course of disease, so as to comprehensively evaluate the characteristics of combined drug use in different baseline populations. Third, set up research centers in European, American, and African countries to further understand the role and potential risks of IGU and MP in other ethnic groups. Fourth, improve the scope of efficacy indicators. As important indicators to measure the progress of pSS, ESSPRI, and ESSDII scores should be included in each study, which will better explore the comprehensive benefits of IGU and MP combined treatment. Fifth, add long-term follow-up data to evaluate further the long-term efficacy of IGU combined with MP in the treatment of pSS, comprehensively evaluate the benefits and risks of IGU combined with MP, and provide a basis for clinical rational drug use.

Conclusions

IGU combined with MP was effective in reducing autoimmune response (IgG, IgA, IgM) and inflammatory response (ESR, PLT), reducing clinical symptoms and disease activity (ESSPRI, ESSDAI), and improving the functional status of exocrine glands (SIT) in patients with pSS. The safety of the "IGU+MP" may be equivalent to that of the "HCQ+MP". IGU combined with MP has the potential to treat pSS, but the above conclusions remain to be validated in a large sample randomized double-blind trial.

Informed Consent

Not applicable.

Ethics Approval

Not applicable.

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